A Multi-Site Break through Cancer Trial: Phase II Study Investigating Dual Inhibition of BCL2 and Menin in AML MRD Using the Combination of Venetoclax and Revumenib (Trial In Progress)

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BREAK THROUGH CANCER

Abstract

Background and Significance: Measurable residual disease (MRD) represents the fundamental driver of relapse and mortality in acute myeloid leukemia (AML). However, there are currently no established approaches to address this unmet need. Our central hypothesis is that targeting vulnerabilities associated with specific leukemia genotypes will eradicate MRD and prevent disease relapse. Break Through Cancer is a collaboration between our centers aimed at making progress in the deadliest cancers by stimulating radical clinical and laboratory research collaboration.

The menin-KMT2A interaction is a critical dependency in acute leukemias caused by rearrangement of the Lysine methyl transferase (*KMT2Ar*) or Nucleoporin 98 (*NUP98r*) genes, or mutation of the Nucleophosmin 1 gene (*NPM1mt*). Revumenib (previously SNDX-5613), is a potent, oral, selective inhibitor of this interaction with an established safety and efficacy in refractory leukemias with these genotypes (Issa GC, Nature 2023). Additionally, *KMT2Ar* or *NPM1mt* leukemias can undergo BCL2-dependent apoptosis, and dual Bcl-2 and menin inhibition led to synergistic activity in *KMT2Ar* or *NPM1mt* leukemia models (Carter BZ, Blood 2021; Fiskus W, BCJ 2022). Therefore, we designed this study investigating the combination of revumenib and venetoclax to eradicate MRD in these AML subtypes (NCT06284486).

Study Design and Methods: This is a single arm, open label, multicenter, phase I/II investigator-initiated study. Patients (pts) age ≥ 12 years with weight ≥ 45Kg, and known history of *NPM1mt*, or *KMT2Ar*, or *NUP98r* AML with MRD ≥ 0.1% identified by multiparameter flow cytometry (MFC) using central testing would be eligible; no morphologic evidence of AML (blasts <5%) in first remission following high intensity therapy or at least 2 cycles of low intensity therapy, or in second remission following any therapy. Up to 12 pts will be enrolled on the phase I, using 3+3, with escalating doses of revumenib and a target dose of 163 mg PO Q12h (with strong CYP3A inhibitor) or 276 mg PO Q12h (without strong CYP3A inhibitor) days 1-28, with venetoclax 400 mg (target dose) PO daily, days 1-14.

The primary objective of the phase I is to determine safety, and the recommended phase II dose. The primary objective of the phase II is to assess the efficacy of venetoclax and revumenib in clearance of MRD (conversion to undetectable by central MFC) within 8 cycles. Up to 14 pts will be included on the phase II portion of the study. With a sample size of 20 pts (Phase II + RP2D in Phase I), the power is 76% assuming an MRD clearance of 30% (based on QUAZAR trial, Roboz et al. Blood 2022) against a null rate of 8%, by a two-sided Fisher's exact test at a significance level of 0.05. We plan to monitor futility and toxicity where enrollment will be stopped early if >95% probability that the MRD conversion rate is < 30% or there is >90% probability that the unacceptable toxicity rate >20%.

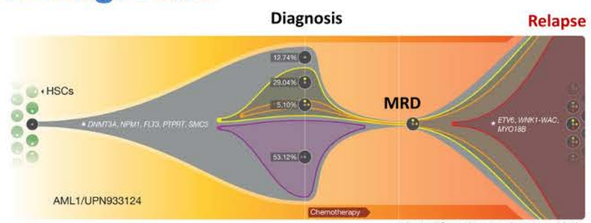
Secondary objectives include assessment of duration of response, event-free and overall survival and concordance of genetic and flow MRD. This trial includes longitudinal collection of samples, with exploratory objectives focused on improving MRD detection using cell-free DNA, single-cell mutation analysis and cytometry by time of flight. In addition, we aim to use various models in addition to patient samples to improve understanding of MRD biology and identify novel susceptibilities.

Accrual is planned at MD Anderson, Dana Farber, Memorial Sloan Kettering, and Johns Hopkins. This study may identify a novel strategy to eradicate MRD using combination targeted therapies which may decrease recurrence and improve remission duration. In addition, this study could improve detection of MRD, and our understanding of MRD biology.

Introduction

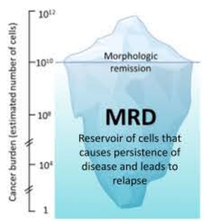
- For decades, AML treatment went unchanged until improved genomic and molecular characterization → advent of targeted therapies
- However, marginal improvement in outcomes of AML (5-year survival of 31.7% - SEER), especially for older patients
- MRD represents the fundamental driver of relapse and mortality in AML.

Background



Adapted from Ding et al. Nature 2012

- **Our central hypothesis is that targeting vulnerabilities associated with specific leukemia genotypes will eradicate MRD and prevent disease relapse.**
- **Break Through Cancer** is a collaboration between our centers aimed at making progress in the deadliest cancers by stimulating radical clinical and laboratory research collaboration.
- The menin-KMT2A interaction is a dependency in *KMT2Ar* or *NUP98 or NPM1mt.*

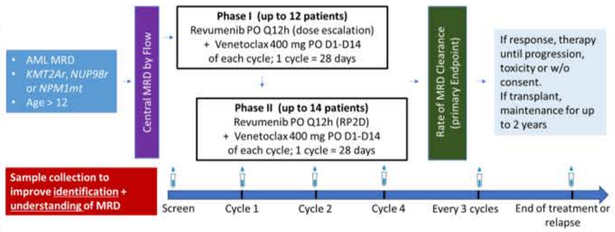


BCL-2 + menin inhibition → eradication of bulk and stem/progenitor cells and improved survival in preclinical models (Carter, Blood 2021).

Dana-Farber Cancer Institute · Johns Hopkins Medicine · Massachusetts Institute of Technology · MD Anderson Cancer Center · Memorial Sloan Kettering Cancer Center

Study Overview

- This is a single arm, open label, multicenter, phase I/II investigator-initiated study (NCT06284486).
- Patients (pts) age ≥ 12 years with weight ≥ 45Kg, and known history of *NPM1mt*, or *KMT2Ar*, or *NUP98r* AML with MRD ≥ 0.1% identified by multiparameter flow cytometry (MFC) using central testing at MSKCC (28-color flow with limit of quantification at 10^{-4}).



Eligibility Criteria

Inclusion:

- Age ≥ 12 years with weight ≥ 45Kg.
- ECOG performance status of ≤ 2.
- Leukemia status:
  - Known history *of NPM1mt*, or *KMT2Ar*, or *NUP98r* AML.
  - Bone marrow assessment showing no leukemia by morphology (blasts <5%) in first remission following high intensity chemotherapy or at least 2 cycles of low intensity therapy (e.g. hypomethylating agent or low-dose cytarabine-based), or in second remission following any therapy, with MRD ≥ 0.1% identified by multiparameter flow cytometry using central lab testing.
  - No clinically active extramedullary disease.
- EF> 40%, adequate hepatic and renal functions

Exclusion:

- Prior treatment with a menin inhibitor.
- Participants who are expected to receive standard therapy (either intensive or hypomethylating agent and venetoclax) with continued tolerability and benefit.
- Participants who are expected to be able to proceed with stem cell transplantation within the next 30 days.
- QTc >450 msec for males and QTc >470 msec for females using the Fridericia Formula.

Study Objectives

Primary Objectives:

- Phase I: To determine the safety, tolerability, and recommended phase II dose (RP2D) of the combination of revumenib and venetoclax for patients with AML and MRD.
- Phase II: To assess the efficacy of the combination of venetoclax and revumenib in clearance of MRD in patients with AML.

Secondary Objectives:

- To assess overall survival (OS), relapse-free survival (RFS), event-free survival (EFS) and duration of response (DOR).
- To determine clinical flow and genetic MRD concordance rate.

Exploratory Objectives:

- To evaluate molecular and cellular markers that may be predictive of antitumor activity and/or resistance.
- To correlate MRD negativity with clinical outcomes (survival and relapse risk).
- To evaluate concordance of standard and novel MRD assays.

Study Design

- Up to 12 patients planned in phase I, using 3+3 design
- Escalating doses of revumenib and a target dose of 163 mg PO Q12h (with strong CYP3A inhibitor) or 276 mg PO Q12h (without strong CYP3A inhibitor) days 1-28, with venetoclax 400 mg (target dose) PO daily, days 1-14.
- **The primary objective of the phase II is to assess the efficacy of venetoclax and revumenib in clearance of MRD (conversion to undetectable by central MFC) within 8 cycles.**
- Sample size of phase II of 20 patients (Phase II + RP2D in Phase I)
  - The power is 76% assuming an MRD clearance of 30% (based on QUAZAR trial, Roboz et al. Blood 2022) against a null rate of 8%, by a two-sided Fisher's exact test at a significance level of 0.05.
- Plan to monitor futility and toxicity where enrollment will be stopped early if >95% probability that the MRD conversion rate is < 30% or there is >90% probability that the unacceptable toxicity rate >20%.

Study Progress

- Activated in October 2024 and enrolling patients at MD Anderson.
- As of November 2024, one patient has been enrolled.
- Planned activation at MSKCC, Johns Hopkins and DFCI expected in the first quarter of 2025.
- Plan to complete accrual by end of 2026.

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MON-4265-2a

ASH2024